NITRODERIVATIVES AS DRUGS FOR DISEASES HAVING AN INFLAMMATORY BASIS

* * * * *

The present invention relates to compounds and the use thereof for diseases affecting the digestive apparatus, in particular the intestinal tract, specifically colites, gastrites, enterites, duodenites and hepatopathies of various nature (on a viral, immune, dismetabolic basis due to intoxications from drugs such as paracetamol and other analgesic, antibiotic, antitumoural, antidepressive drugs, etc., alcohol, etc.).

The digestive apparatus diseases are very diffused. While the therapy of the peptic ulcer has generally reached efficacy, the same cannot be said for other diseases affecting the digestive apparatus. For example it is known that yearly in the Unites States more than 25 million people suffer diseases affecting liver and gall-bladder and more than 26,000 people die owing to chronic hepatopathies and cirrhosis. Generally the therapeutical treatment is widely unsatisfatory. Among the compounds used for these treatments interferon α-2b can be mentioned, which allows the recovery in about 30-40% of the cases affected by chronic hepatitis B and 20-25% of those affected by chronic hepatitis C.

However the interruption of the treatment causes a recidivism in 50-80% of the patients. Only 10% of the cases of hepatitis B are satisfactory with interferon α-2b. Another compound used for these pathologies is ribavirin, however the efficacy is not yet well known. Other used compounds are vaccines, which however are used only in the prophylaxis.

For the cirrhosis treatment there are generally no

effective compounds. At present the treatment is above all of support and it can consist in a suitable diet, alcohol abstinence or in the administering of diuretics or vitamins.

The therapeutic treatment is generally unsatisfactory for the diseases affecting the intestinal tract such colites, duodenites, enterites. For example the therapy with 5-amino salicylic acid and derivatives thereof is not fully effective. The use of steroidal compounds (for example prednisolone and the like) can cause toxic symptoms or serious side effects.

It must be added that generally the pathologies on an inflammatory basis, such as those above described affecting the digestive apparatus, are considered precancerous forms, since they can evolve into tumoural processes. In the same way for the pathologies on an inflammatory basis, which can concern different systems such the urogenital, respiratory apparatuses, the skin districts, etc.

Therefore the treatment of these pathologies of inflammatory nature has a critical importance also in the prevention and in the treatment of tumoral diseases.

The need was felt to have available compounds active in diseases on an inflammatory basis, in particular those affecting the digestive apparatus and for the prevention and/or treatment of the tumoral processes related to the above diseases.

It has been surprisingly found by the Applicant that it is possible to solve the above technical problem with specific nitroderivatives as described hereunder.

An object of the present invention is the use, for diseases on an inflammatory basis, of nitroderivatives or salts thereof having the following general formula (I):

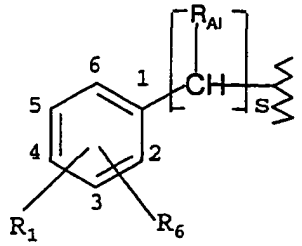
$$A\text{-}X_1\text{-}L\text{-}(W)_p\text{-}NO_2 \qquad (I)$$

wherein:

p is an integer equal to 1 or 0;

A = R-T_1-, wherein

R is the radical of a precursor drug and it has the following formulas:



(AI)

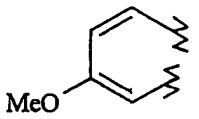
s is an integer and is 1 or 0;

R_{AI} is H, CH_3;

R_1 is $OCOR_3$, R_3 being a C_1-C_5 linear or branched radical, $NHCOR_3$, wherein R_3 has the above meaning, or R_1 is OH, $CH_2CH(CH_3)_2$, phenyl, benzoyl, 4,6-dichlorophenylamino;

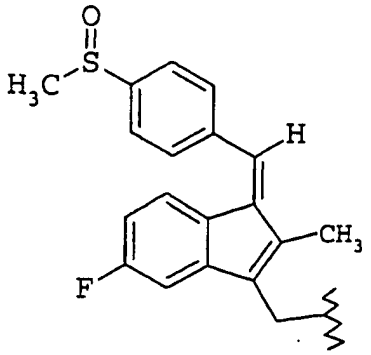
R_6 is H, or an halogen atom, preferably fluorine;

or R_1 and R_6, when are located in the adjacent positions 4 and 5 of the aromatic ring of formula (AI), form the radical of following formula (AIa):



(AIa)

or R can be the following formula:



(AII)

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

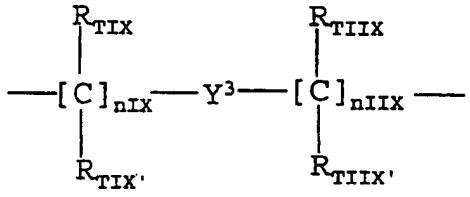
X_1 = $-T_B-Y-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI}= $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the 0 or 1 value; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

Y is a bivalent linking group selected from the following:



(II)

wherein:

nIX is an integer in the range 0-3, preferably 1;

nIIX is an integer in the range 1-3, preferably 1;

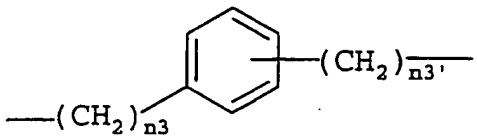
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or a C_1-C_4 linear or branched alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring having 5 or 6 atoms, containing one or two nitrogen atoms,

an alkylene group R' wherein R' is a C_1-C_{20} linear or branched when possible, preferably

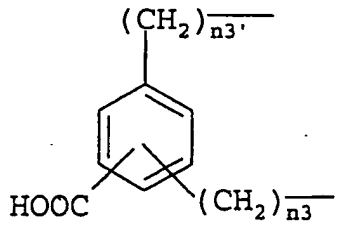
having from 2 to 6 carbon atoms, optionally substituted with one or more of the following groups: $-NHCOR_3$, wherein R_3 is as above, $-NH_2$, -OH or

- a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chains R', R' being as above, one or more carbon atoms of the cycloalkylene ring can optionally be substituted by heteroatoms; or



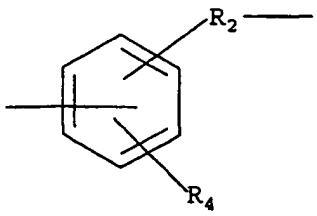
(III)

wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;



(IV)

wherein n3 and n3' have the above meaning,

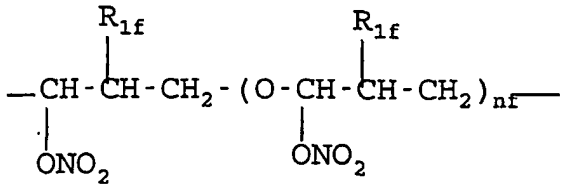


(V)

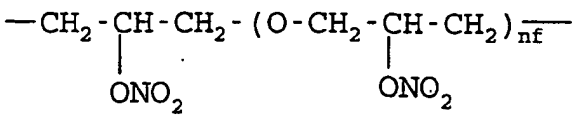
wherein

R_4 is hydroxy, hydrogen, R_5O- alkoxy wherein R_5

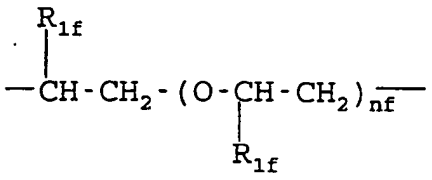
is a C_1-C_{10} linear or branched or cyclic alkyl group, preferably R_5 is a methyl group;
R_2 is a C_2-C_{10} linear or branched alkenylene group which can contain one or more double bonds, preferably R_2 is the ethenylene group (-CH=CH-); or



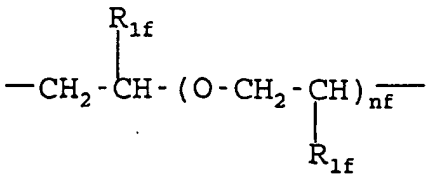
(VI)



(VII)



(VIII)



(IX)

wherein R_{1f} = H, CH_3 and nf is an integer from 0 to 6; preferably from 0 to 4;

L = covalent bond, or L = X , X being as above, or L = CO;

W = Y_TO wherein Y_T has the same meanings of Y but in the compound of formula (I) Y_T is equal to or different from Y. Preferably Y_T is different from Y.

The diseases on an inflammatory basis are those particularly affecting the digestive apparatus, preferably the intestinal tract, such as for example colites, gastrites, enterites, duodenites; besides epatopathies and tumoral processes related to diseases on an inflammatory basis.

When in formula (AI), R_1 is an acetyloxy group in position 2 of the ring, s = 0 and R_6 = H and the free valence of the radical R is saturated with the -COOH group, the compound is known as Acetylsalicylic Acid,

when in formula (AI) R_1 is an hydroxyl group in position 2 of the ring, s = 0 and R_6 = H and the free valence of the radical R is saturated with a -COOH group, the compound is known as Salicylic Acid,

when in formula (AI) R_1 is an acetylamino group in position 4 of the ring, s = 0 and R_6 = H and the free valence is saturated with an -OH group, the compound is known as Paracetamol,

when in formula (AI) R_1 is $CH_2CH(CH_3)_2$ in position 4 of the ring, s = 1, R_{AI} = CH_3 and R_6 = H and the fre valence is saturated with a -COOH group, the compound is known as Ibuprofen,

when in formula (AI) R_1 is phenyl and it is in position 4 of the ring, s = 1, R_{AI} = CH_3 and R_6 = F in position 3 and the free valence is saturated with a -COOH group, the compound is known as Flurbiprofen,

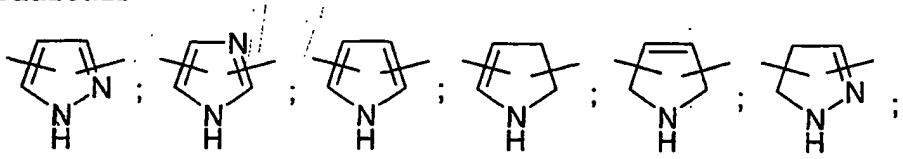
when in formula (AII) the free valence is saturated with the -COOH group, the compound is known as Sulindac;

when in formula (AI) R_1 and R_6 are the radical of formula (AIa) and they are connected with the positions 4 and 5 of the ring, s = 1, R_{AI} = CH_3, R_6 = H and the free valence is saturated with a -COOH group, the compound is known as Naproxen;

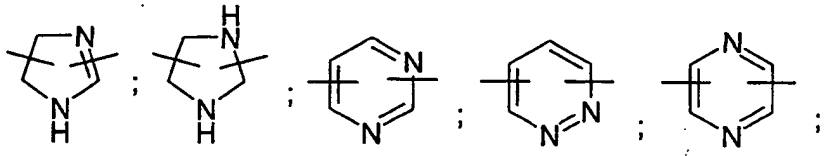
when in formula (AI) R_1 is a benzoyl radical in position 5 of the aromatic ring, s = 1, R_{AI} = CH_3, R_6 = H and the free valence is saturated with a -COOH group, the compound is known as Ketoprofen;

when in formula (AI) R_1 = 2,6-diclorofenilammino in position 2 of the ring, s = 1, R_{AI} = H, R_6 = H and the free valence is saturated with a -COOH group, the compound is known as Diclofenac.

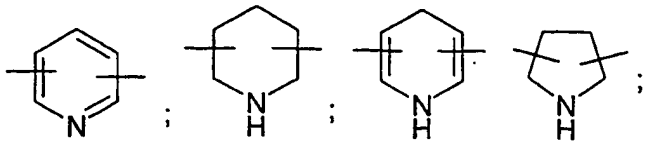
Preferably Y^3 in formula (II) of the linking group Y of X_1 in formula (I) is selected from the following bivalent radicals:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

Preferably Y^3 is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the

two free valences respectively in the positions 2 and 6, or 2 and 3 or 2 and 5 with respect to the heteroatom.

The preferred of Y^3 is Y12 (pyridyl) substituted as above indicated. The bonds can also be in an unsymmetrical position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) can be 3,5-disubstituted.

The preferred compounds are those wherein in formula (I):

- when in formula (AI) s = 0 and R_6 = H:
  - R is a radical of formula (AI) wherein the substituent R_1 is in position 2 of the aromatic ring, and it is selected between acetyloxy or hydroxyl, or it is an acetylamino group and then it is in position 4; $-T_1-T_B-$ is a -CO-O- or -O-OC- ester group; Y of the radical X_1 is a bivalent linking group selected from the following:
    - a radical of formula (III) as above, wherein n3 = 0 and n3' = 1,
    - a radical of formula (II) as above wherein Y^3 is Y12 as above defined,
    - a radical of formula (VIII) as above wherein R_{1f} is hydrogen and nf = 1;

    T_{B1} = -O-, L = covalent bond; p = 0;
  - R is a radical of formula (AI) wherein the substituent R_1 is in position 2 of the aromatic ring, and it is selected between acetyloxy or hydroxyl, or it is an acetylamino group and then it is in position 4; $-T_1-T_B-$ is a -CO-O- or -O-OC- ester group; Y of the radical X_1 is a bivalent linking group having formula (V) as above wherein R_4 is a methoxyl group and R_2 = -CH=CH-; $-T_{B1}-L-$ is a -CO-O- or -O-OC- ester group; p = 1; W = YO wherein Y is $-(CH_2)_4-$ or $-(CH_2)_3-$;

- R is a radical of formula (AI) wherein the substituent R_1 is in position 4 of the aromatic ring, and it is acetylamino; $-T_1-T_B-$ = -O-CO-; Y of the radical X_1 is $-(CH_2)_3-$; $-T_{B1}-L-$= -O- (L = covalent bond); p = 0;
- R is a radical of formula (AI) wherein the substituent R_1 is in position 4 of the aromatic ring, and it is acetylamino; $-T_1-T_B-$ = -O-CO-; Y of the radical X_1 is an ethylene group substituted with an acetylamino group: $-CH(NHCOCH_3)-CH_2-$; $-T_{B1}-L-$ = -S-CO-; p = 1; W = YO wherein Y is $-(CH_2)_3-$;

when in the formula (AI) s = 1:

- R is a radical of formula (AI), R_6 = H or F in position 3 of the ring, R_1 = $CH_2CH(CH_3)_2$ or phenyl in position 4, $-T_1-T_B-$ is a -CO-O- ester group; Y of the radical X_1 is a bivalent linking group having formula (V) as above wherein R_4 is a methoxyl group and R_2 = -CH=CH-; $-T_{B1}-L-$ is a -CO-O- ester group; p = 1; W = YO wherein Y is $-(CH_2)_3-$;

- when in formula (I) R is a radical of formula (AII), $-T_1-T_B-$ = -CO-O-; Y of the radical X_1 is a bivalent linking group selected from the following:
  - a radical of formula (II) as above wherein Y3 is Y12 as above,
  - $-(CH_2)_4-$;
  - $-T_{B1}-$= -O-, L = covalent bond; p = 0.

The preferred compounds according to the present invention are those wherein:

- the drug radical has formula (AI) and the compounds of formula (I) are the following:

2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester,

2-(hydroxy)benzoic acid 3-(nitrooxymethyl)phenyl ester,

2-(acetyloxy)benzoic acid 4-(nitrooxymethyl)phenyl ester,

2-(hydroxy)benzoic acid 4-(nitrooxymethyl)phenyl ester,
2-(acetyloxy)benzoic acid 2-(nitrooxymethyl)phenyl ester,
2-(hydroxy)benzoic acid 2-(nitrooxymethyl)phenyl ester,
2-(acetyloxy)benzoic acid 6-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 6-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
2-(acetyloxy)benzoic acid 5-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 5-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 3-(nitrooxymethyl)-2-methyl pyridinyl ester hydrochloride, or nitrate,
trans-3-[4-[2-acetyloxybenzoyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy)butyl ester,
trans-3-[4-[2-hydroxybenzoyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy)butyl ester,
4-(nitrooxy)butanoic acid 4-(acetylamino)phenyl ester,
trans-3-[4-(4'-nitrooxybutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester,
3-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl ester,
4-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl ester,
2-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl ester,
5-(nitrooxymethyl)pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
6-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
3-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetylamino)phenyl ester,
5-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetylamino)phenyl ester,

5-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetylamino)phenyl ester,

6-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetylamino)phenyl ester,

3-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetylamino)phenyl ester,

3-[(2-nitrooxy)ethyloxy]propanoic acid 4-(acetylamino)phenyl ester,

trans 3-[4-(4'-nitrooxybutyryloxy)-3-methoxy]phenyl-2-propenoic acid 4-(acetylamino)phenyl ester,

2-(acetylamino)-3-(4-nitrooxybutyryl)-3-mercaptopropanoic acid 4-(acetylamino)phenyl ester,

trans-3-[4-[α-methyl-4-(2-methylpropyl)phenylacetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitrooxybutyl ester,

trans 3-[4-[2-fluoro-α-methyl(1,1'-biphenylyl)-acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitrooxybutyl ester,

(S) 6-metoxy-α-methyl-2-naphtalenacetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenyl ester,

(S) 6-metoxy-α-methyl-2-naphtalenacetic acid 3-(nitrooxy methyl)phenyl ester,

(S) 6-metoxy-α-methyl-2-naphtalenacetic acid 6-(nitrooxy methyl)-2-methylpyridinil ester,

(S,S)-N-acetyl-S-(6-metoxy-α-methyl-2-naphtaleneacetyl) cysteine 4-(nitrooxy)butyl ester,

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 6-(nitro oxymethyl)-2-methylpyridinil ester chloridrate,

- The drug radical has formula AII and the compounds of formula (I) are the following:

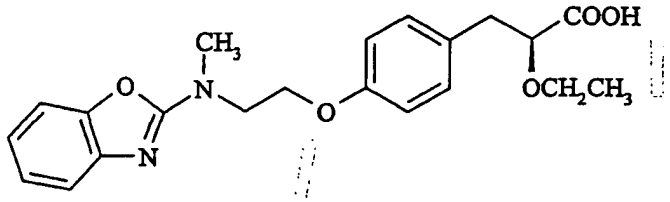
(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl] methylene]-1H-inden-3-acetic acid 4-(nitrooxy)butyl ester,

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl] methylene]-1H-inden-3-acetic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester hydrocloride, or nitrate,

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl] methylene]-1H-inden-3-acetic acid 5-(nitrooxymethyl)-2-methylpyridinyl ester hydrocloride, or nitrate,
(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl] methylene]-1H-inden-3-acetic acid 3-(nitrooxymethyl)-2-methylpyridinyl ester hydrocloride, or nitrate.

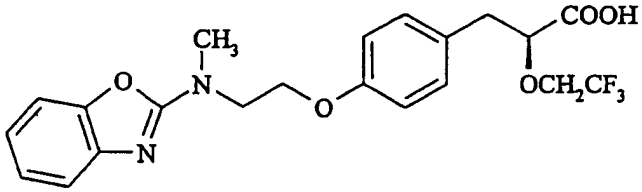
Other precursors of the general formula A = R-T_1- wherein the free valence is saturated with -OH, that can be used for obtaining the compounds of formula (I) are the following:

(S)-Benzenepropanoic acid, 4-[2-(2-benzoxazolylmethyl amino)ethoxy]-.-(2-ethoxy) of formula (XX):



(XX)

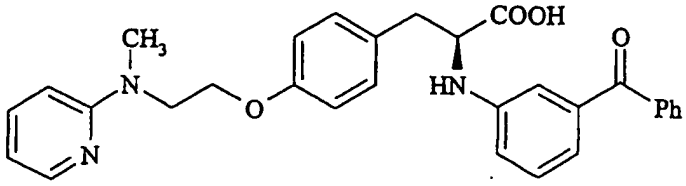
(S)-Benzenepropanoic acid, 4-[2-(2-benzoxazolylmethyl amino)ethoxy]-.-(2,2,2-trifluoroethoxy) of formula (XXI):



(XXI)

Compounds (XX) and (XXI) are described in PCT Patent Application WO 97/25042;

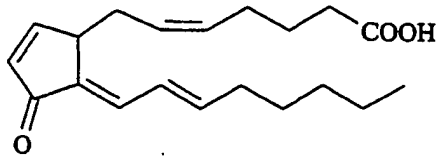
L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(methyl-2-pyridinyl amino)ethyl] of formula (XXII):



(XXII)

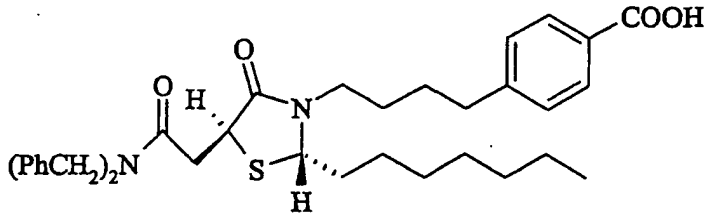
The above compound is described in PCT Patent Application WO 97/31907;

Prosta-5,9,12,14-tetraen-1-oic acid, 11-oxo-, (5Z,12E, 14E) (15-Deoxy Δ12,14-prostaglandin) of formula (XXIII):



(XXIII)

(2S,5S)-4-(4-(4-carboxyphenyl)butyl)-2-heptyl-4-oxo-5-thiazolidine N,N-dibenzylacetamide of formula (XXIV):



(XXIV)

The above compound is described in Proc. Natl. Acad. Sci 1999, 96(11), 6102-6106.

The bivalent radical precursors of formula (II) are for example those wherein the two free valences are saturated with two hydroxyl groups, or with one hydroxyl group and one carboxylic group. These compounds are available on the market.

When the drug radical R or the bivalent radical Y and/or W as above defined contain one or more asymmetric carbon atoms, the corresponding precursors can be used in the synthesis of the compounds of the invention both in racemic form and as single optical isomers.

When in the molecule of the compounds of the invention (formula I) a salifiable functional group, for example an amino or heterocyclic nitrogen is present, it is possible to use the corresponding salts. The latter are obtained by reaction in organic solvent such as for example acetonitrile,